BMJ

RESEARCH

Effectiveness of earlier antenatal screening for sickle cell disease and thalassaemia in primary care: cluster randomised trial

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Cite this as: *BMJ* 2010;341:c5132
doi:10.1136/bmj.c5132

ABSTRACT

Objective To evaluate the effectiveness of offering antenatal screening for sickle cell disease and thalassaemia in primary care as a way of facilitating earlier uptake of screening.

Design Partial factorial cluster randomised controlled trial.

Setting 25 UK general practices from deprived inner city areas.

Participants Anonymised data on all pregnant women attending participating practices during a six month period before randomisation and a seven month period after randomisation. This included 1708 eligible women.

Intervention Practices were randomised to three groups for seven months: parallel testing in general practice (tests for sickle cell disease and thalassaemia offered to both parents when pregnancy was first reported); sequential testing in general practice (tests offered to mothers when pregnancy was first reported, and subsequently to the partners of women who were found to be carriers); and midwife care (tests offered to mothers at first consultation with a midwife).

Main outcome measures The primary outcome (available for all women) was the proportion of eligible women screened before 10 weeks' (70 days') gestation. Secondary outcomes were an offer of screening to women before 10 weeks' gestation, gestational age at testing, mean interval from first visit to the general practice visit to screening, and women's knowledge of the carrier status of their baby's father before 77 days' (11 weeks') gestation. The study was designed to detect a 20% absolute increase in screening uptake. Cluster level analyses were adjusted for age group, parity, ethnic group, primary care organisation, and number of general practitioners per practice.

Results Data were analysed for 1708 eligible women. In the midwife care arm, 2% (9/441) of women were screened before 10 weeks' gestation compared with 24% (161/677) in the GP parallel testing arm and 28% (167/590) in the GP sequential testing arm. The estimated adjusted difference between the midwife care and GP parallel testing arms was 16.5% (95% confidence interval 7.1% to 25.8%; P=0.002) and between the midwife care and GP sequential testing arms was 27.8% (14.8% to 40.7%; P<0.001). By 26 weeks' gestation the proportion of women screened across the three trial arms was similar (81%). The proportion of women who knew the carrier status of the baby's father by 11 weeks' gestation was 0% (0/441) in the midwife care arm, 2% (13/677) in the GP parallel testing arm (P=0.003), and 1% (3/590) in the GP sequential testing arm (P=0.374).

Conclusion Offering antenatal screening for sickle cell disease and thalassaemia as part of consultations for pregnancy confirmation in primary care increases the proportion of women screened before 10 weeks' gestation. Even with intervention, however, only a minority of women were screened before 10 weeks. Additional interventions should be considered to achieve testing early in pregnancy for most women wanting such tests so that couples with affected pregnancies have less time pressure to choose options, which may include termination of the pregnancy.

Trial registration Current Controlled Trials ISRCTN00677850.

INTRODUCTION

Inherited disorders of haemoglobin are autosomal recessive traits and include sickle cell disorders and thalassaemia. These are the most common conditions caused by single gene defects, with 5% of the world's population being carriers and about 300 000 births worldwide affected by severe forms of the disease each year.[1] Northern and western Europe now have more affected conceptions than southern Europe as a result of recent migrations.[2] The 59th World Health Assembly recently urged member states to implement

equitable and effective programmes for the prevention and management of sickle cell anaemia.[3] Policy options for antenatal screening for sickle cell disease and thalassaemia concern solely the offer of reproductive choice in the absence of early treatment to improve outcomes. Policy options in the United Kingdom have been evaluated in two systematic reviews.[4 5] The results of these reviews informed the introduction in England of a universal antenatal screening policy in areas of high prevalence in 2004. This policy has a target of offering antenatal screening for sickle cell disease and thalassaemia by 10 weeks' gestation to enable the completion of prenatal diagnostic testing by 13 weeks for those who want it.[6] The rationale for this is based on evidence from two studies.[7 8] Both showed an association between gestational age and uptake of prenatal diagnosis for haemoglobinopathy: women in earlier stages of pregnancy were more likely to take up the offer of prenatal diagnosis. It is postulated that by offering prenatal diagnosis sufficiently early in pregnancy, women can have time to make an informed, less time pressured decision about their options, which might include termination.

A recent study provided the first population based estimate of gestational age at screening for sickle cell disease and thalassaemia. The results showed that most women present to their family doctors early in pregnancy but that delays before screening are long. On average, women attended their general practice to confirm their pregnancies at 7.6 weeks' gestation (75% by 10 weeks). The median gestational age at testing, however, was 15.3 weeks, a median delay of 6.9 weeks.[9] The proportion of women screened by 10 weeks was 4.4%. Evidence from two descriptive studies suggests that the early offer of testing is associated with earlier testing.[10 11] Current practice is to offer sequential testing to fathers: fathers are offered carrier testing only when the mother has been identified as a carrier. This policy has the potential to delay the assessment of the carrier status of couples during pregnancy and hence impact on risk to the fetus.

We investigated the utility of offering tests to both parents simultaneously to reduce the delay in assessing the carrier status of couples. Our objectives were twofold: to assess whether offering antenatal screening for sickle cell disease and thalassaemia at the first visit for confirmation of pregnancy in primary care leads to earlier testing, and to assess whether indirectly offering testing to fathers at the same time leads to earlier knowledge of the couples' carrier status.[12]

Interventions to offer antenatal screening for sickle cell disease and thalassaemia

Parallel testing in general practice

Women were offered screening when they first reported their pregnancy in primary care. Fathers were offered screening at the same time

Sequential testing in general practice

Women were offered screening when they first reported their pregnancy in primary care. Fathers were offered screening only if the mother was identified as a carrier

Midwife care

Women were offered screening by the midwife at the booking visit. Fathers were offered screening only if the mother was identified as a carrier

METHODS

The trial took place in two UK primary care trusts containing 123 general practices. The two primary care trusts are ranked among the most deprived in England (sixth and 13th out of 354), with about 40% of their populations being classified as representing ethnic minority groups.[13] An estimated 6% of the pregnant women in the study areas carry a significant haemoglobin variant.[14] Women who become pregnant usually first report their pregnancy to the general practice through a consultation with the family doctor (the pregnancy confirmation visit). The women are then referred to specialist maternity services and receive a consultation with a midwife (the booking visit). This visit may take place in a community setting. Other models of care, such as direct access to midwifery led care, do occur, but none of the women used this model of care during the trial period. A universal screening policy was operating in the study's general practices—that is, all pregnant women were offered testing for haemoglobin disorders.

We used a cluster randomised controlled design, with general practice as the unit of randomisation, firstly, to assess the effectiveness of three methods for offering universal antenatal screening for sickle cell disease and thalassaemia (box) and, secondly, because it would be difficult to arrange for pregnant women attending the same practice to receive different models of care. One of the interventions, midwife care, was the standard pattern of care in the United Kingdom at the time of the trial.

Recruitment and randomisation

We sent each of the 123 general practices a written invitation to take part in a trial examining the feasibility, effectiveness, and acceptability of offering antenatal screening for sickle cell disease and thalassaemia in primary care. The methods used to recruit and retain practices in the trial are described elsewhere.[15] Twenty nine practices expressed an interest in the trial and 27 agreed to participate. Two practices withdrew before randomisation.

Participating practices were allocated to intervention groups after they had entered the run-in period for data collection. Data were collected at each practice during this period for a minimum of six months to obtain information on at least 33 pregnancies. The run-in period varied between six and 11 months. The trial statistician (MG) independently determined to which intervention the 27 practices would be allocated, using minimisation,[16] stratifying for primary care trusts and number of partners at the practice (1 or 2, ≥3). The trial manager (ED) informed the participating practices of the group to which they had been allocated.

Participants

We collected anonymised data on all pregnant women attending the participating practices during a six

month period before randomisation and a seven month period after randomisation. Data were also collected for screening outcomes until 26 weeks' gestation. Women were eligible for inclusion in the analysis if they wanted to continue their pregnancies, their pregnancies were less than or equal to 19 weeks and six days' gestation at their first visit to primary care, there was no written record of their sickle cell and thalassaemia carrier status in primary care, and their estimates of gestational age based on the date of their last menstrual period were considered by them to be certain.

We excluded women who confirmed their pregnancies at later gestations because of the difficulties with arranging a termination of pregnancy. All women, regardless of ethnicity, were offered screening and were eligible for the trial. All fathers of eligible pregnancies in practices allocated to the parallel testing group were eligible to be offered the test at the same time as the women. Likely response rates for fathers were estimated from previous studies offering genetic tests in primary care.[17] A CONSORT diagram showing the flow of practices and participants through the trial is given in fig 1.

Measures

The primary outcome was uptake of screening by women before 10 weeks' (70 days') gestation. Gestational age at test uptake was calculated from the first day of the last menstrual period to the date of venesection for antenatal screening for sickle cell disease and thalassaemia. These data were collected anonymously from practices and were available for all eligible pregnancies. Secondary outcomes were an offer of screening to women before 10 weeks' gestation; gestational age at testing, as calculated by time from the date of the last menstrual period to screening; mean interval from first visit to the general practice to screening; and women's knowledge of the carrier status of their baby's father by 11 weeks' (77 days') gestation. The offer of screening for sequential testing and parallel testing groups was determined from the practices' electronic records and for midwife care from the date of the booking visit, as recalled by the women.

Sample size

We estimated that, as for a trial with two arms, we required data on 264 women attending eight general practices (33 women per practice) in each trial group to give sufficient power to detect an absolute difference of 20% in the proportion of women undergoing screening by 10 weeks' gestation in different trial arms, assuming 90% power and 5% significance. Our initial estimate, based on unpublished audit data from South Thames Regional Health Authority, suggested that 30% of women were screened by 10 weeks' gestation. The data monitoring committee (see web extra on bmj.com) reviewed the sample size calculation before the start of the intervention phase of the study. A revised estimate was informed by data collected during a cohort study, representing the run-in phase of the trial, providing updated estimates for screening uptake and the intraclass correlation coefficients for screening uptake under usual care.[9] The trial had sufficient power to detect a difference between trial arms of 20%, assuming a revised rate of 4.4% of women screened by 10 weeks' gestation in the midwife care arm. Sample size calculations assumed an intraclass correlation coefficient of 0.03, based on a review of 31 studies in primary care, in which 75% of such coefficients were less than 0.032.[18] Analysis of data from the run-in data collection phase of the present trial produced an intraclass correlation coefficient of 0.036 for all women and 0.068 for eligible women.[9] Repeating the initial sample size calculations using an intraclass correlation coefficient of 0.07 indicated that data were required from 1173 eligible women. Available information was insufficient for a sample size calculation on testing the fathers.

Recruitment and training

The research team invited the practices to participate using a research information sheet for practices.[19] Expenses of about £3000 (€3600; $4700) were available for each practice. We used research activity agreements, detailing a payment schedule based on deliverables, to administer these payments.[15]

We offered general practitioners, nurse practitioners, and practice nurses in the intervention practices an evidence based training package using clinical scenarios.[20] This training outlined the topics to be covered when offering the screening test. These included that the test was optional, the purpose of the test, the meaning of possible results, and subsequent options. These are in line with the recommendations of the UK National Screening Committee and with the standard training offered to midwives. Midwives in the midwife care practices were given locally provided standard training in offering the screening test. All underwent training in the research protocol. General practitioners offered the test during consultations at which women first reported their pregnancies. For women accepting offers, blood tests were ordered separately from other routine antenatal blood tests. General practitioners did not cover other aspects of the routine booking in pregnancy.

Interventions

GP parallel testing

General practitioners, practice nurses, and nurse practitioners offered screening to eligible women at their first visit for pregnancy confirmation. A verbal explanation supplemented by written information produced by the NHS sickle cell and thalassaemia screening programme was provided. If the father was present, the test was also offered to him. If the father did not attend or was not registered at the practice, women were invited to offer the baby's father testing using a take home pack. The pack contained written information on the test, information on several local test centres (primary care, local hospital, sickle cell and thalassaemia centre) where the test could be done, and a request

form. The fathers' samples were analysed as soon as they were received by the laboratory.

GP sequential testing

General practitioners, practice nurses, and nurse practitioners offered screening to eligible women at their first visit for pregnancy confirmation. Fathers of the babies in this study group were offered sequential testing—that is, offered a test only if the mother was found to be a carrier of sickle cell disease or thalassaemia. Local counsellors in sickle cell disease offered testing to fathers, in line with the National Health Service sickle cell and thalassaemia screening programme.

Midwife care

Women were offered screening at the booking appointment. This appointment is the first antenatal check and is usually carried out by a community midwife; in this trial either at the woman's home, in a community based clinic, or at a hospital. The fathers of the babies in this study group were offered sequential testing.

In all groups blood samples were taken according to local protocols. For participants in the general practice (parallel and sequential testing) groups, blood samples were usually taken just for this test; for participants in the midwife care group, blood samples were usually taken as part of a set of routine blood tests.

Data collection

Data were collected during the run-in period before the intervention phase for a minimum of six months, or longer if necessary, so that data were collected on a minimum of 33 eligible pregnancies per practice. The intervention phase lasted for seven months, or longer if necessary, so that data were collected on a minimum of 33 pregnancies per practice. Data collection for the run-in and intervention phases took place between June 2005 and August 2007.

Fidelity to the research protocol was assessed by comparing maternity referrals with records of pregnancies received by the research team. Fidelity to the clinical protocol in the intervention groups was assessed by comparing records of pregnancies received by the research team with the practice records of women offered testing in primary care. Discrepancies were discussed and resolved with participating practices. We repeated data abstraction for a sample of the primary outcome measures and found it to be reliable.

Statistical analysis

To estimate the difference between intervention groups in proportions of women screened before 10 weeks' gestation, we implemented a cluster level analysis, using linear regression of the practice specific proportions on intervention group. We used the method of minimum variance weights to allow for varying numbers of eligible women between practices.[21] Analyses were adjusted for the proportion of eligible women screened before 10 weeks' gestation in the run-in period, the age group of eligible women at the practice, the proportion that were primiparous, the proportion in higher risk ethnic groups, the number of partners at the practice (1 or 2, ≥3), and primary care trust. Thus the primary measure of effect is the adjusted difference in uptake of screening before 10 weeks' gestation, between trial arms. Analyses are described in more detail in a full trial report.[20] Individual level analyses to estimate odds ratios or mean differences using the method of generalised estimating equations gave consistent results and are also reported in the trial report.[20] Among 1708 eligible women, 1376 were screened before 182 days' (26 weeks') gestation. We sought screening records by 26 weeks for the remaining 332 women, up to the end of the study, but none were found. This included 74 women who had left their practices at an undetermined date.

Cluster level analyses were also implemented for the mean gestational age at uptake of screening and mean delay from pregnancy confirmation visit to uptake of screening. We used exact logistic regression to compare screening uptake by fathers because the numbers of events were small.

The intraclass correlation coefficient of a binary outcome is associated with prevalence. These correlations estimated by analysis of variance for the proportion screened before 10 weeks' gestation were 0.038 for midwife care, 0.061 for GP parallel testing, and 0.142 for GP sequential testing.

RESULTS

Four practices from the two primary care trusts did not agree to randomisation, resulting in 119 eligible practices being invited to participate in the trial (fig 1). Overall, 29 practices participated, two as pilot sites and 27 in the trial. Two practices withdrew and 25 completed the trial. Data from the run-in phase before the interventions were implemented are described elsewhere.[9]

In the intervention phase 2421 pregnancies were identified across 25 practices, of which 1708 met the eligibility criteria (table 1). The trial groups did not differ in age, parity, or proportion of women confirming pregnancy before 70 days. In all three groups (parallel testing, sequential testing, and midwife care), over 70% of women had confirmed their pregnancies in primary care before 10 weeks' gestation. Ethnicity differed slightly among the trial arms, with a higher proportion of South Asian and South East Asian women in the GP sequential testing arm than the other trial arms, and more African and African Caribbean women in the GP parallel testing arm than the other trial arms. In the run-in phase, uptake of screening before 10 weeks' gestation was highest (7%) in the practices assigned to GP parallel testing compared with 4% for midwife care and 3% for GP sequential testing.

More women were screened before 10 weeks' gestation in both of the general practice intervention groups (parallel and sequential testing) than in the midwife care group. In the midwife care group, 2% (9/441) of women were screened before 10 weeks' gestation compared with 24% (161/677) in the GP parallel testing group and 28% (167/590) in the GP sequential testing

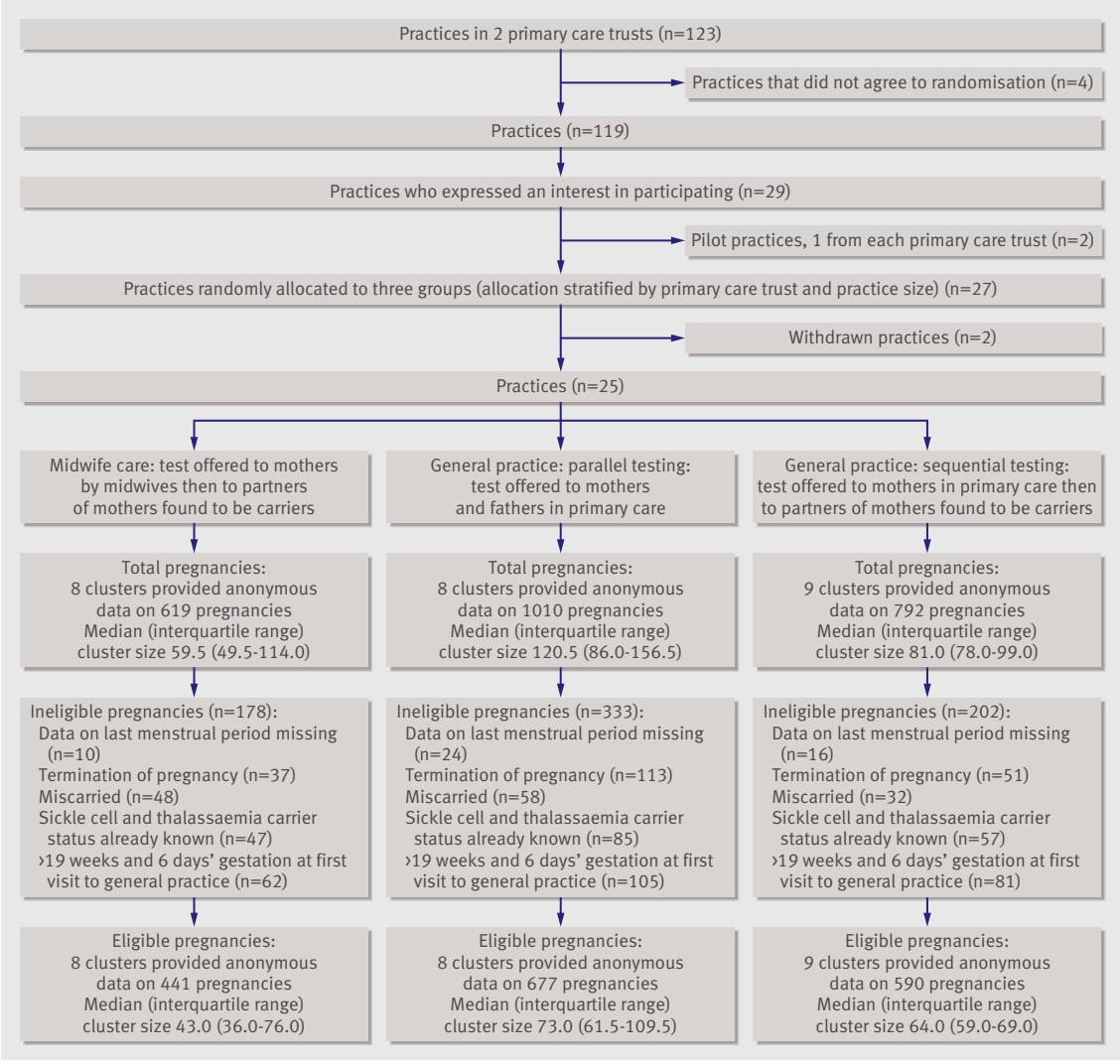

Fig 1 | **Flow of practices and participants through study**

group (table 2 and fig 2). After adjusting for pre-intervention screening performance, age, parity, and ethnicity, compared with midwife care the uptake of screening before 10 weeks' gestation was 16.5% (95% confidence interval 7.1% to 25.8%; P=0.002) for GP parallel testing and 27.8% (14.8% to 40.7%; P<0.001) for GP sequential testing (table 3). Although the uptake of screening at 10 weeks seemed to be slightly higher in the sequential testing arm than in the parallel testing arm, this was not maintained at later gestational ages (fig 2). Adjustment for pre-intervention screening performance was quantitatively more important in the parallel testing group; nevertheless, uptake of screening in the two intervention arms was not significantly different from each other at 10 weeks' gestation (P=0.119). Changes were considered across practices and the results were not driven by any one practice. Details of the trial outcomes for each general practice are in the full report.[20]

In the midwife care group, 3% (3/90) of women were offered screening before 10 weeks' gestation compared with 47% (321/677) in the GP parallel testing group and 48% (281/590) in the GP sequential testing group. In the adjusted analysis, the increases in proportion of participants offered the test before 10 weeks' gestation compared with midwife care was 39.2% (26.0% to 52.4%; P<0.001) for GP parallel testing and 44.2% (26.6% to 61.9%; P<0.001) for GP sequential testing (table 2).

The mean gestational age at screening for women with tests done in the midwife care group was 118 days compared with 94 days in the GP parallel testing group and 90 days in the GP sequential testing group. In the adjusted analysis, the differences compared with midwife care were 15.5 days for GP parallel testing (P=0.008) and 21.8 days for GP sequential testing (P=0.003; table 3 and fig 2).

The mean interval between the pregnancy confirmation visit and screening was 60 days in the midwife care group. This delay was reduced by 18.0 days in the GP parallel testing group and by 21.5 days in the GP sequential testing group (table 3 and fig 2).

The overall pattern of uptake for screening was similar for GP sequential testing and GP parallel testing groups (fig 2). Further analyses showed no differences

Table 1 | Characteristics of participants. Values are frequencies (percentage of eligible participants in group) unless stated otherwise

Characteristics	Midwife care sequential	General practice		P value*
		Parallel testing	Sequential testing	
No of general practices	8	8	9	—
Primary care trust A: B	4:4	4:4	5:4	Stratifier
No of general practitioners at practice (1-2: ≥3)	3:5	3:5	3:6	Stratifier
Run-in phase: No of eligible participants	336	594	460	—
Pregnancy confirmation visit <10 weeks' (70 days') gestation	255 (76)	458 (77)	347 (75)	0.941
Screening test <10 weeks' gestation	12 (4)	39 (7)	12 (3)	0.275
Mean (interquartile range) gestational age at screening (days)	111 (91-130)	104 (87-120)	110 (88-129)	0.318
Mean (interquartile range) duration from pregnancy confirmation to screening (days)	53 (34-72)	48 (32-63)	49 (36-65)	0.460
Intervention phase				
All participants†	619	1010	792	—
Eligible participants†‡	441 (71)	677 (67)	590 (74)	—
Median (interquartile range) age (years)	28.0 (23.6-32.8)	28.0 (23.9-32.2)	29.1 (25.2-33.8)	0.250
Primiparous	241 (55)	392 (58)	307 (52)	0.650
Pregnancy confirmation visit <10 weeks' gestation	323 (73)	505 (75)	464 (79)	0.386
Ethnic group:				
Northern European	76 (17)	101 (15)	121 (21)	0.001
South Asian and South East Asian	93 (21)	103 (15)	224 (38)	
African and African Caribbean	84 (19)	180 (27)	93 (16)	
Southern European and other European	70 (16)	138 (20)	72 (12)	
Other ethnicity	14 (3)	25 (4)	22 (4)	
Mixed ethnicity	12 (3)	13 (2)	13 (2)	
Not known	92 (21)	117 (17)	45 (8)	
Ineligible participants†:				
Data on last menstrual period missing	10	24	16	—
Termination of pregnancy	37	113	51	—
Miscarriage	48	58	32	—
Carrier status known	47	85	57	—
First visit ≥140 days' gestation	62	105	81	—

*Test for difference between groups.
†87 had two or more exclusion criteria.
‡Values are number (percentage of all participants).

between these groups for offer or uptake of screening before 10 weeks' gestation, gestational age at uptake of screening, or delay between confirmation of pregnancy and screening. By 26 weeks' gestation the proportions of women screened across the three groups were similar. Overall, 81% of women were screened by 26 weeks' gestation (table 2).

The uptake of screening by fathers was 8% (51/677) in the GP parallel testing group, 3% (16/590) in the GP sequential testing group, and 3% (13/441) in the midwife care group. The proportion of women who knew the carrier status of the baby's father by 77 days' (11 weeks') gestation was 0% (0/441) in the midwife care group, 2% (13/677) in the GP parallel testing group (P=0.003), and 1% (3/590) in the GP sequential testing group (P=0.374).

Overall uptake of screening before 26 weeks' gestation was similar in northern Europeans and in women of "higher risk" ethnicity. In adjusted analyses, ethnicity was not associated with uptake of screening before 10 weeks' gestation or 26 weeks' gestation and mean gestational age at the time of screening. In adjusted analyses, however, women of higher risk ethnicity had a shorter delay from the visits for pregnancy confirmation to testing: the mean difference from northern Europeans was about 7.4 days (95% confidence interval 2.5 to 12.3).

Overall uptake of screening before 10 weeks' gestation was 15% in women aged 24 years and younger but 21% in women aged more than 32 years. The mean difference in gestational age at screening (adjusted for trial arm, primary care trust, number of doctors at practice, parity, high risk ethnicity, and run-in screening performance) between women aged 24 or less and those aged more than 32 years was 11.3 days (6.2 to 16.4; P<0.001). This was associated with later visits for pregnancy confirmation among the younger mothers who, on average, confirmed their pregnancies about 10 days later than older mothers. Screening outcomes were generally similar for primiparous and multiparous women.

No adverse events occurred in this trial.

DISCUSSION

Offering antenatal screening for sickle cell disease and thalassaemia at a visit for confirmation of pregnancy in primary care increased the proportion of women screened before 10 weeks' gestation. It also reduced

Table 2 | Screening outcomes by intervention group. Values are numbers (percentages) unless stated otherwise

Variables	No (%)		
	Midwife care (n=441)	Parallel testing in general practice (n=677)	Sequential testing in general practice (n=590)
Women's uptake of screening <10 weeks' (70 days') gestation	9 (2)	161 (24)	167 (28)
Offer of screening <10 weeks' gestation	3/90* (3)	321 (47)	281 (48)
Mean (interquartile range) gestational age at screening uptake† (days)	118 (101-134)	94 (66-118)	90 (61-113)
Mean (interquartile range) interval from pregnancy confirmation visit to screening uptake (days)	60 (42-79)	35 (7-59)	31 (5-54)
Screening uptake of fathers	13 (3)	51 (8)	16 (3)
Women who knew carrier status of baby's father by 11 weeks' (77 days') gestation	0 (0)	13 (2)	3 (1)
Women's uptake of screening <26 weeks' (182 days') gestation	324 (73)	571 (84)	481 (82)

*Offer of test ascertained for 90 respondents only.[22]
†Women who were screened <26 weeks' gestation.

the delay between women presenting for pregnancy and tests being offered and carried out. The offer did not alter the overall proportion of women screened, indicating that the different methods of offering the test did not affect whether women underwent testing, but the stage in pregnancy when they received the offer. Offering testing to fathers at the pregnancy confirmation visit was associated with low uptake of screening. Even after intervention, only a few women were screened before 10 weeks' gestation. It is not known if the delay in screening in women allocated to midwife care resulted from a delay in seeing a midwife or if there were additional delays between the consultation and testing in that intervention arm.

Unanswered questions and future research

The level of screening uptake observed in this population was lower than anticipated when the trial was designed. This is partly explained by the exclusion of women whose carrier status was already known. In addition, substantial variations in uptake of screening between family practices, ranging from 0% to 22%, were observed in this study.[20] Taking these two factors, as well as sampling error, into account it is not surprising that an unpublished audit might generate a result that differed from our population based estimates. None the less, our findings serve to emphasise the low levels of uptake for screening early in pregnancy and the need for additional interventions to raise these further. Development of suitable interventions may require qualitative research to understand the reasons why women attend early or not, as well as understanding the organisational and professional barriers and facilitators of early testing. Some studies suggest that general practitioners attribute failure to test to lack of time, language barriers, or lack of training.[20] When the test was offered, the organisation of phlebotomy services did not always facilitate same day testing. Developments in testing technology may allow the use of blood spots for antenatal screening for sickle cell disease and thalassaemia,[22] which may reduce the need for phlebotomy services and thus reduce some of the observed delay in testing.

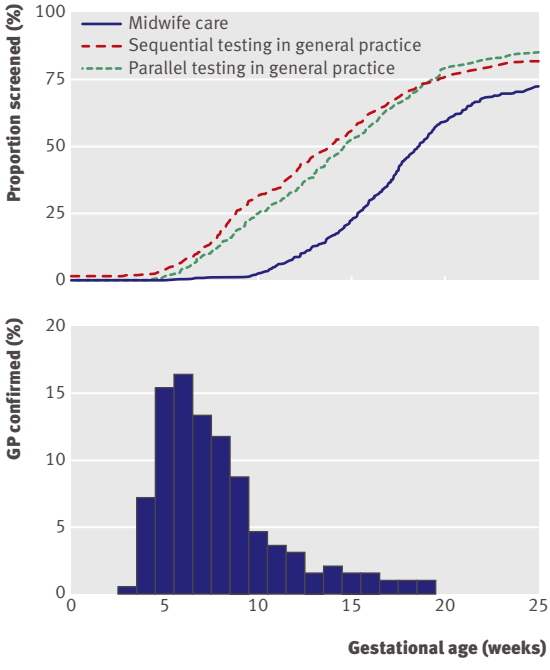

Fig 2 | Proportion of women screened by gestational age according to intervention group (upper panel) and distribution of pregnancy confirmation visits to general practices for all groups combined (lower panel)

The potential consequences of an earlier offer of screening in terms of offering and carrying out subsequent invasive procedures earlier in pregnancy was not evaluated in this trial because to do so would have required a larger sample size. This supposition therefore requires investigation. Nor did this trial investigate the views of women who may have undergone screening knowing that they would not terminate an affected fetus.

Reproductive choice includes options to decline or accept prenatal diagnosis. Screening programmes need to ensure that choices to decline and to accept prenatal diagnosis are made with appropriate information and in line with individual attitudes. Uptake in the absence of informed choice is an undesirable outcome.[23] Informed choice was assessed in this trial and is reported separately.[20] Although there were no differences in rates of informed choice across the trial groups, the overall rates of informed choice were low, with about a third of women classified as making an informed choice.

Table 3 | Adjusted cluster level analysis showing estimated effect of intervention on screening outcomes, with midwife care as reference group

	Parallel testing in general practice (n=677)		Sequential testing in general practice (n=590)	
Outcome	Estimate (95% CI)	P value	Estimate (95% CI)	P value
% increase in uptake of screening <10 weeks' (70 days) gestation*	16.5 (7.12 to 25.8)	0.002	27.8 (14.8 to 40.7)	<0.001
% increase in offer of screening <10 weeks' gestation†	39.2 (26.0 to 52.4)	<0.001	44.2 (26.6 to 61.9)	<0.001
Mean reduction in days of gestational age at screening‡	−15.5 (−26.4 to −4.63)	0.008	−21.8 (−34.8 to −8.80)	0.003
Mean reduction in days from pregnancy confirmation to screening§	−18.0 (−26.3 to−9.7)	<0.001	−21.5 (−32.5 to −10.4)	0.001
% increase in uptake of screening <26 weeks' gestation¶	3.80 (−7.93 to 15.54)	0.502	9.83 (−2.30 to 22.0)	0.105

*Adjusted for model 1 and proportion of women screened before 10 weeks' gestation in run-in period.
†Adjusted for age group, parity, proportion of high risk ethnic groups, primary care trust, and number of doctors at practice (model 1).
‡Adjusted for model 1 and mean gestational age at screening in run-in period.
§Adjusted for model 1 and mean time interval from pregnancy confirmation to screening in run-in period.
¶Adjusted for model 1 and uptake of screening before 26 weeks' gestation in run-in period.

Comparison with other studies

In a previous observational study in which antenatal screening for sickle cell disease and thalassaemia was offered in primary care, lower uptake of testing was observed compared with uptake by women receiving midwife care. This seemed to reflect failures within the organisation and delivery of screening.[11] Such failures were avoided in the current trial: offering testing in primary care did not alter the likelihood of testing in this trial. This suggests that uptake of screening is not influenced by offers early in pregnancy or by the professional group offering the test.

We estimated, based on limited data, that there would be a 20% increase in uptake of screening from 30% to 50%. In this study, baseline uptake of screening was much lower than anticipated. However, the sample size was re-estimated and reviewed by the data monitoring committee, based on a cohort study for baseline in the same population, with data for some 1500 women. The trial provides data for a further 1700 women. We did not have confidence in the 30% figure as indicated previously.

The trial found limited benefit from offering tests to fathers at the same time as those to mothers, given few fathers underwent testing. This is in contrast to the 90% uptake of carrier testing of fathers for cystic fibrosis observed in a similar trial in primary care.[17] Several differences between the trials may account for this contrast: the current trial offered testing to the biological father rather than to the woman's partner and required blood testing rather than a salivary sample. In the current trial the biological father was not always registered at the same general practice as the woman, or was unavailable for other reasons. A further difference was that the current trial was carried out in an area with high levels of social and material deprivation. Data were not recorded on the number of fathers who attended primary care with pregnant women. The testing of fathers required a blood sample. Blood tests were offered to fathers in the parallel testing group in one of two ways in primary care: face to face when present at the consultation or, if not present, with the assistance of the women, who were given a pack containing information on screening and how to access testing to give to the baby's father. Uptake of testing by fathers before 11 weeks' gestation (51/677) may seem low because uptake of maternal testing by 70 days was low (161/677).

Strengths and limitations of the study

The trial design was robust and the likelihood of bias was low: allocation to trial arms was randomised, with allocation concealed to participants before the intervention and the primary end point was reported for all participants. The trial was carried out in the United Kingdom in areas with high prevalence of sickle cell disease and thalassaemia. This raises questions about the generalisability of the findings to other countries and areas with lower prevalence and to screening for other conditions. The extent to which the trial results can be applied in other contexts will probably depend on the existence and organisation of primary care services. Further questions about the generalisability arise as the outcomes were achieved under trial conditions: the offer of screening was for a limited period and the research team contacted practices on a regular basis to encourage fidelity to the protocol.

The general practices observed were not randomly selected from the 123 general practices in the two primary care trusts studied and therefore may not be representative of the practices in these trusts. The variables on which data are available show that participating practices were similar to other practices in the study primary care trusts for practice size, deprivation, and patient ethnic group. In addition, the study primary care trusts were chosen to represent geographical areas with a high prevalence of sickle cell disease and thalassaemia and therefore may not be representative of other areas. The primary care trusts represent deprived inner city areas where general practice lists are longer than those in suburban or rural areas and primary care services are generally less well organised.[20]

The trial arms differed in more ways than just the timing at which testing was offered. Those in the intervention groups were trained by the research team whereas those in the midwife care group were offered locally provided standard training.[20] Midwives presented the test in the midwife care group, whereas general practitioners presented the test in the other two groups. The similar rates of uptake of testing in the three groups suggest, however, that any differences in

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many women present early in pregnancy to their family doctor, but there are long delays before screening is offered

Evidence from descriptive studies suggests that early testing is associated with higher uptake of prenatal diagnosis for sickle cell disease and thalassaemia

WHAT THIS STUDY ADDS

Offering screening for sickle cell disease and thalassaemia in primary care at the time of pregnancy confirmation leads to earlier testing, although most women who are tested during pregnancy are unscreened by 10 weeks' gestation

The likelihood of being tested during pregnancy is unaffected by offering screening earlier in the pregnancy

The impact of earlier screening on uptake of prenatal diagnosis remains unknown

test presentation related to profession did not affect uptake. Information on the screening test provided to the pregnant women in all three trial groups was the same—namely, literature on NHS screening programmes.[24] The number of carriers detected was too small to evaluate effects on reproductive choices. It is acknowledged that uptake of testing by fathers may be associated with ethnicity, but this is unlikely to be relevant in this trial because overall the uptake of testing by fathers was low. The small number of fathers tested raises questions about the generalisability of the results of such testing.

The date of testing was not the same as the date women were informed of their test results. The delay between pregnancy confirmation and women being informed of their test results is likely to be greater than the delay between pregnancy confirmation and testing.

The analysis had limitations: only a modest number of practices participated, with small numbers of women per practice, consequently limiting the analyses. We used a cluster level analysis of the practice specific means and proportions to facilitate presentation of differences in proportions. Analyses were weighted for varying cluster sizes using minimum variances weights.[20] This requires estimation of the intraclass correlation coefficient (ρ) for each trial group. The number of practices may not have been sufficient to provide precise estimates of ρ. Differences in estimates were, however, negligible and showed no difference in interpretation from using analyses that were unweighted or weighted for cluster size. We also carried out analyses at individual level, using the method of generalised estimating equations, incorporating adjustments to allow for the small number of practices. These results were consistent with the cluster level analyses. Since data for testing of fathers and maternal carriers were sparse, we used exact logistic regression, but analyses implemented using ordinary logistic regression with robust standard errors gave consistent results.

As this was a three arm trial and the two intervention groups, sequential testing and parallel testing, might not have had truly independent effects, reported P values should be interpreted cautiously. The analysis plan did not, however, include adjustment of P values for multiple testing.

Conclusions

The results of this trial suggest that offering testing to women in primary care has some potential to increase the uptake of screening in early pregnancy. Fully realising this potential requires three things; firstly, that women need to report their pregnancies early; secondly, that women need to be offered screening early in pregnancy; and thirdly, that the carrier status of couples needs to be confirmed within days of identifying women carriers, in those who want to proceed with further testing. Achieving this requires systems designed to achieve timely, effective, and sensitively delivered services. A potentially more effective way to achieve early decision making is through preconceptual screening.[25]

We thank the general practices who participated in this trial and Erin Reid, Katrina Brown, Tony Ades, Pelham Barton, Verna Davis, Barbara Wild, and Moira Dick. ED is now quality improvement lead at NHS Sickle Cell and Thalassaemia Screening Programme, King's College School of Medicine, London. See web extra on bmj.com for details of the committees involved with this trial.

Contributors: TMM and ED defined the research question. TMM, ED, MG, SB, and TER participated in the design of the trial and intervention. ED, KB, ER, and VT collected the data under the trial management of ED. MG wrote the statistical analysis plan and did the statistical analyses. All authors participated in the acquisition and analysis of data, in critical revision of the manuscript, and have seen and approved the final version. TMM is the guarantor.

Funding: This trial was funded by the UK Department of Health through its Health Technology Assessment Programme (grant No 03/02/03) "Antenatal screening for haemoglobinopathies in primary care: a cluster randomised trial to inform a simulation model (Acronym: SHIFT—Screening for Haemoglobinopathies In First Trimester)." The funding body had no role in the study design, data collection, analysis, interpretation, or writing of the report. All authors had full access to all study data and were jointly responsible for the decision to submit for publication.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any company for the submitted work; no financial relationships with any companies that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Royal Free Hospital ethics committee (05/Q0501/36).

Data sharing: No additional data available. The trial protocol is on the *Lancet* website at www.thelancet.com/protocol-reviews/06PRT-921.

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Accepted: 2 August 2010